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Importance of oral glucose overload test (OGOT) at a specific clinic for advanced CRF stages IV and V

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SUMMARY

A pathological Oral Glucose Tolerance test (OGTT) is an early marker of peripheral insulin resistance. Nevertheless, its utility in nondiabetic patients with CRF stage IV-V is undetermined. ***Aim:*** *We wanted to detect, in a population of non diabetic patients with CRF, the presence of carbohydrates metabolism anomalies, by means of the OGTT and to relate it with metabolic, anthropometric, cardiovascular parameters and renal function. We studied 45 non diabetic patients with advanced CRF (stage IV-V), 26 men, mean age 66.5 years, with average Cockroft-Gault of 23.6 ml/min. We measured weight, height, waist and BMI.* ***Biochemical:*** *glucose, insulin, OGTT, C peptide, lipid profile, HbA1C and Hto. Cardiovascular comorbidity, mean proteinuria and systolic and diastolic blood pressure (6 months pre and post analytical measure) were measured. Pulse pressure was also calculated.* ***Results:*** *47% of the patients presented normal fasting glucose, whereas 53% had isolated impaired fasting glucose (IFG). After the OGTT, 36% of the patients presented impaired glucose tolerance (IGT) and 14% diabetes (> 200 mg/dl). Of the patients with normal fasting glucose, 38% had IGT after OGTT and 5% diabetes. Patients with IFG (n = 24), 33% presented IGT and 21% diabetes. Patients with abnormal OGTT were older (71 ± 13.6* versus *60 ± 18.8 years, p = 0.03), had greater HbA1C (5.6 ± 0.5* versus *5.2 ± 0.3%, p = 0.02), total cholesterol (193 ± 37.7* versus *169.8 ± 44.9 mg/dl, p = 0.03), pulse pressure (63.4 ± 14.5 versus 52.3 ± 9.7 mmHg, p = 0.0001) and greater prevalence of ischemic heart disesase (28%* versus *5%, p = 0.05). Creatinine Clerance negatively correlated with the OGTT (r = -0.39, p = 0.01) and plasma creatinine positively with fasting insulin (r = 0.33, p = 0.02) and C-peptide (r = 0.42, p = 0.006). Urinary Proteins were correlated with fasting glucose (r = 0.30, p = 0.04), C-peptide (r = 0.52, p = 0.001), triglycerides (r = 0.36, p = 0.01) and with the HOMA-IR index (r = 0.30 p = 0.05)* ***Conclusion:*** *Fasting Glucose did not predict OGTT results in patients with CRF. For this reason, we think that the OGTT can be very useful tool to identify states of «prediabetes» and diabetes in patients with CRF, specially in those whose present an elevated Pulse Pressure, age greater than 65 years, hyperlipidaemia and HbA1C above 5.2%. The early detection of these metabolic anomalies, may lead to intensify dietetic and pharmacological measures directed to delay or to attenuate the appearance of diabetes and its serious complications in a population in which the cardiovascular risks factors are very elevated.*

Key words: ***Oral glucose tolerance test. Chronic renal failure. Diabetes. Insulin resistance.***

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IMPORTANCIA DEL TEST DE SOBRECARGA ORAL A LA GLUCOSA (TSOG) EN UNA CONSULTA ESPECÍFICA DE IRC AVANZADA ESTADIO IV Y V

RESUMEN

Un TSOG patológico es un marcador precoz de resistencia periférica a la insulina. ***Objetivos:*** *Identificar, en una población de pacientes no diabéticos con IRC avanzada marcadores clínicos asociados a un TSOG patológico, para reconocer a cuáles de nuestros pacientes debemos realizarle dicha prueba.* ***Material y métodos:*** *Estudiamos 45 pacientes no diabéticos, 26 varones, 66,5 años, con IRC avanzada estadio IV y V. Se midió peso, talla, cintura, IMC, glucosa, insulina, TSOG, péptido C, lípidos, HbA1C y Hto. Comorbilidad cardiovascular, proteinuria y presión de pulso medias (6 meses).* ***Resultados:*** *47% de los pacientes presentó una glucemia basal normal (GBN) y 53% glucemia basal anómala (GBA). Tras el TSOG, un 36% de los pacientes presentó intolerancia oral a la glucosa (IOG) y un 14% una glucemia mayor de 200 mg/dl (DM). De los pacientes con GBN, 38% tuvieron IOG tras el TSOG y el 5% DM. De los pacientes con GBA (n = 24), 33% presentó IOG y 21% DM. Los pacientes con TSOG patológico tenían más edad (71 ± 13,6* vs *60 ± 18,8 años, p = 0,03), mayor HbA1C (5,6 ± 0,5* vs *5,2 ± 0,3%, p = 0,02), mayor colesterol total (193 ± 37,7* vs *169,8 ± 44,9 mg/dl, p = 0,03), mayor presión de pulso (63,4 ± 14,5* vs *52,3 ± 9,7 mmHg, p = 0,0001) y mayor prevalencia de cardiopatía isquémica (28%* vs *5%, p = 0,05). El GFR se correlacionó negativamente con el TSOG (r = -0,39, p = 0,01) y la proteinuria con la glucemia basal (r = 0,30, p = 0,04), péptido C (r = 0,52, p = 0,001), triglicéridos (r = 0,36, p = 0,01) e índice de HOMA (r = 0,30 p = 0,05). Tras el modelo de curvas COR, la edad, la HbA1C, el colesterol total y la Presión de Pulso, tuvieron un área bajo la curva significativa para predecir TSOG patológico.* ***Conclusión:*** *La glucemia basal en ayunas no predijo un TSOG patológico en pacientes con IRC avanzada, por ello, creemos que la realización del TSOG puede ser muy útil para identificar estados de «prediabetes» y diabetes en estos pacientes, especialmente en aquellos que presentan una Presión de Pulso elevada, una edad mayor de 65 años, dislipemia y HbA1C mayor de 5,2%.*

Palabras clave: ***Sobrecarga oral a la glucosa. Insuficiencia renal crónica. Diabetes oculta. Resistencia periférica a la insulina.***

INTRODUCTION

An abnormal oral glucose overload test (OGOT) is a marker of peripheral insulin resistance (PIR), detects occult diabetes, and is associated with high cardiovascular morbimortality in the general population.[1-5] However, in non-diabetic patients with advanced chronic renal failure, its use has not been well established.[6-8]

We aimed at studying a population of non-diabetic patients with advanced CRF (stages IV and V) with the following objectives: 1) to detect the presence of carbohydrate metabolism impairments (occult diabetes and carbohydrate intolerance) by means of OGOT, and analyze the associations with metabolic, anthropometrical, cardiovascular, and renal function parameters; 2) To identify the clinical factors associated to an abnormal OGOT, in order to identify what patients should have this test done.

PATIENTS AND METHODS

Patients

We undertook a cross-sectional study on 45 non-diabetic patients with advanced chronic renal failure (CRF), stages IV and V, not entering dialysis (creatinine clearance < 30 mL/min), followed at the pre-dialysis specific clinic of the Nephrology Department at the University Hospital of Canarias, for the period comprised between January 1st and December 31st of

2005. Informed consent was obtained from all patients.

Exclusion criteria were: age older than 80 years, active neoplasic disease, intestinal inflammatory disease, liver disease, bronchial disease, or sever cardiopathy, recent acute disease (less than 3 months), weight loss greater than 10% in the previous 3 months before the study, and hypothyroidism.

Concomitant therapies at the time of the study, such as hypolipidemic agents (statins and Fibrates), ACEIS, ARA-II, beta-blockers, diuretics, erythropoietin and anti-aggregants were registered. No patient received treatment with steroids or anabolic agents.

We also gathered patients' cardiovascular comorbidity from a personal history of ischemic heart disease, congestive heart failure episodes, peripheral and cerebral vascular disease, defined by standard criteria.[9]

Finally, mean systolic and diastolic blood pressures from the clinic readings of the 6 months before and after laboratory work-up were calculated in order to know the mean pulse pressure (systolic BP – diastolic BP) during that period. A pulse pressure (PP) higher than 63 mmHg is associated with higher cardiovascular morbimortality risk.[10,11]

Methods

Height and weight were taken for each patient by means of accurate scales and height readers. Body mass index (BMI = Weight (kg)/Height (m^2)) was obtained from height and weight. Waist was measured by means of an inextensible tape measure at the navel, with the patient standing according to the usual technique.

Biochemical determinations were done by automated standardized methods (Hitachi modular auto-analyzer, Roche) at 8 a.m. after 12-h fasting. We measured: BUN, glucose, creatinine, bicarbonate, uric acid, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, insulin by enzyme immunoassay (Axsym Insulin 2003, Abbott Co., Tokyo, Japan), C peptide by chemiluminescence, HbA1C by HPLC (high performance liquid chromatography), PTH-i by chemiluminescence (Immulite 2000 Intact PTH, Diagnostic Products Co., Los Angeles, Ca, USA). Hematocrit and hemoglobin were measured by Coulter. Creatinine clearance was calculated by means of the Gault-Cockcroft formula: Kcr (mL/min) = (140-age) * Weight (kg)/(plasma Cr * 72). The obtained value was multiplied by 0.85 in women.[12]

Mean proteinuria in 24-h urine was calculated from 6 months before and after laboratory work-up.

Oral glucose overload test (OGOT): briefly, it was performed with 75 g of glucose mixed in 400 mL of water, taken within 5-10 minutes. A baseline sample was drawn and another one at 120 minutes to determine plasma glucose.

Definitions[13,14]

Normal fasting baseline glycemia: up to 100 mg/dL; abnormal fasting baseline glycemia (ABG): 100-126 mg/dL; and diabetes mellitus when fasting baseline glycemia was > 126 mg/dL.

After OGOT, we defined as a normal test: glycemia < 140 mg/dL; oral glucose intolerance (OGI): glycemia: 140-200 mg/dL; and diabetes mellitus: glycemia > 200 mg/dL.

In order to have in depth knowledge on carbohydrate impairments, we calculated the HOMA-R index (Homeostasis Model Assessment), which consists in estimating peripheral insulin resistance from a mathematical model that takes into account insulin and fasting baseline glycemia. This model has been validated in diabetic and non-diabetic populations as well as in CRF patients.[15-22] This index is calculated by the Mathews *et al.* equation:[15] Insulin (mU/L) × glucose (mmol/L) / 22.5. Insulin resistance is defined as a HOMA-R index > 3.8 (mU/L × mmol/L) or baseline insulinemia >16 mU/L, which corresponds to the 90th percentile of the reference general healthy Spanish population with normal weight from Ascaso *et al.* work.[16]

Statistical analysis

Descriptive statistics were initially done: numerical variables were expressed as mean plus standard deviation, and qualitative variables as proportions or percentages. When variables were normally distributed (Kolmogorov-Smirnov test) we used parametric tests, and if not, their non-parametric equivalents. Since the sample comprises 45 patients, the differences for a quantitative variable between two groups of patients were analyzed by the Mann-Whitney U test. To check whether there were statistically significant differences between two proportions, we used the chi-squared test or the Fisher exact test when the observed frequencies were small. The relation study between quantitative variables was done by means of the calculation of Pearson's r correlation coefficients. A two-tailed P value lower than 0.05 was considered to be significant. In order to detect factors that independently were associated to an abnormal OGOT, we used ROC (Receiver-Operator Characteristic) curves and the Youden index (J = sensitivity + specificity -1).[23] The software used for the statistical analysis was SPSS 12.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Renal failure causes were: 15.6% nephroangiosclerosis, 24.4% interstitial nephropathy, 4.4% glomerulonephritis, 28.9% unknown, 15.6% polycystic renal disease, 2.2% systemic, and 8.9% other causes.

Patients' characteristics are shown in Table I. According to the ATP III and WHO criteria for diagnosing metabolic syndrome,[13-14, 24] 46.7% of our patients had baseline glycemia >100 mg/dL, 51% overweight, 27% total cholesterol > 200 mg/dL, 29% HDL-cholesterol < 50 mg/dL for women and < 40 mg/dL for men, 24% triglycerides > 150 mg/dL, 54% waist at risk (higher than 102 cm in men and 88 cm in women). As a whole, 30% of our patients had metabolic syndrome.

Forty-seven percent of the patients had normal fasting baseline glycemia (< 100 mg/dL), whereas 53% had ABG. After OGOT, strikingly 36% of the patients had glycemia 140-200 mg/dL, that is to say oral glucose intolerance (OGI) and up to 14% glycemia higher than 200 mg/dL, a criterion for diabetes.

Of patients with normal baseline glycemia (n = 21), 38% had OGI after OGOT and 5% diabetes. Of patients with abnormal baseline glycemia (n = 24), 33% had OGI and 21% diabetes.

Table II. Patients with abnormal OGOT (glycemia at 2 hours ≥ 140 mg/dL) had older age, higher HbA1C, higher total cholesterol, higher pulse pressure, and higher ischemic heart disease prevalence. The remaining parameters analyzed and treatments received did not differ between groups (not shown in the Table). From our work, we highlight a very clinically interesting observation that is baseline fasting glycemia in our patients did not predict the result of the oral glucose overload test.

Table I. General characteristics of the patients

Age (years)	66.5 ± 16.8
Male/Female	26/19
Cockroft-Gault (mL/min/1,73m^2)	23.6 ± 7.3
Proteinuria (g/24 horas)	0.61 ± 0.8
BMI (kg/m^2)	25.4 ± 3.5
Waist (cm)	97.1 ± 14.2
Baseline glycemia (mg/dL)	101.2 ± 11
Baseline insulin (mU/L)	9.7 ± 5.5
HbA1C (%)	5.4 ± 0.4
Baseline C peptide (ng/mL)	4.6 ± 2.4
Triglycerides (mg/dL)	126.8 ± 53
Total cholesterol (mg/dL)	182.6 ± 40
LDL-cholesterol (mg/dL)	97.9 ± 27
HDL-cholesterol (mg/dL)	56.1 ± 16
Uric acid (mg/dL)	7.4 ± 1
HTC (%)	36.4 ± 3
Pulse pressure (mmHg)	57.9 ± 13
% Coronary disease	15
% Congestive heart failure	7
% Peripheral vascular disease	7
% Cerebral vascular disease	9
% Without comorbidity	47
% ACEI/ARA II	64
% Beta-blockers	18
% EPO	53
% Statins/Fibrates	73
% Anti-aggregants	51

BMI: Body mass index. ACEI: angiotensin converting enzyme inhibitors. ARA-II: angiotensin II receptor antagonists. EPO: erythropoietin.

Relevant correlations

Glycemia at 2 hours from OGOT was directly and significantly correlated with age (r = 0.37; p = 0.01) and HbA1C (r = 0.34; p = 0.02), and negatively correlated with creatinine clearance (r = -0.39; p = 0.01).

Baseline glycemia was positively correlated with proteinuria (r = 0.30; p = 0.04) and negatively with age (r = -0.31; p = 0.03).

As an expression of hyperinsulinism, baseline insulin was correlated with triglycerides (r = 0.45; p = 0.002), C peptide (r = 0.77; p = 0.001), BMI (r = 0.34; p = 0.01), waist (r = 0.37; p = 0.01), the number of hypotensive drugs (r = 0.37; p = 0.01), plasma creatinine (r = 0.33; p = 0.02), and negatively with HDL-cholesterol (r = - 0.30; p = 0.04) and age (r = -0.46; p = 0.002). Similarly, the HOMA index was correlated with the same parameters and with proteinuria (r = 0.30; p = 0.04).

HbA1C was correlated with pulse pressure (r = 0.31; p = 0.04), and C peptide was correlated with age (r = - 0.36; p = 0.02), BMI (r = 0.37; p = 0.01), triglycerides (r = 0.46; p = 0.003), creatinine (r = 0.42; p = 0.006) and strikingly with proteinuria (r = 0.50; p = 0.001).

Predictors of OGOT

When developing the model for the ROC curves for the different metabolic and clinical parameters associated with an abnormal OGOT (Figure 1), we observed that age, HbA1C, total cholesterol, and pulse pressure had a significant area under the curve (p < 0.05) (Table III).

Particularly, the cut-off point for age that best predicted an abnormal OGOT was 66 years, with 80% sensitivity, and 53% specificity. For HbA1C, it was a 5.2% value, with 72% sensitivity and 55% specificity; for cholesterol it was 175 mg/dL, with 72% sensitivity and 75% specificity, and finally for pulse pressure it

Table II. Comparison between patients by OGOT

	Normal OGOT (N = 23)	Abnormal OGOT (N = 22)	p
Age (years)	60.1 ± 18.8	71.2 ± 13.6	0.03
HbA1C (%)	5.2 ± 0.3	5.6 ± 0.5	0.02
Total cholesterol (mg/dL)	169.8 ± 44.9	193.1 ± 37.7	0.03
Pulse pressure (mmHg)	52.3 ± 9.7	63.4 ± 14.5	0.0001
Creatinine clearance (mL/min)	22.1 ± 5.1	17.6 ± 8.9	0.055
Baseline disease			NS
% NAE	6	21	
% IN	15	32	
% CGN	4	6.5	
% Unknown	40	26	
% PCRD	20	9	
% Others	15	5.5	
BMI (kg/m^2)	25.8 ± 3.5	25.1 ± 3.6	NS
Waist (cm)	98.3 ± 14.4	96.4 ± 14.5	NS
Coronary heart disease	5%	28%	0.05
Baseline glycemia < 100 mg/dL	50%	50%	NS

OGOT: oral glucose overload test. Normal OGOT: after oral glucose overload, glycemia within 2 hours < 140 mg/dL. Abnormal OGOT: after oral glucose overload, glycemia within 2 hours ≥ 140 mg/dL. NAE: Nephroangiosclerosis, IN: Interstitial Nephropathy. CGN: Chronic Glomerulonephritis. PCRD: Polycystic renal disease. BMI: Body mass index.

was 66 mmHg, with 62% sensitivity and 55 % specificity.

DISCUSSION

This study confirms a high prevalence of carbohydrate metabolism impairments and occult diabetes mellitus among our patients with advanced CRF, detected only after the performance of an OGOT. The Experts Committee for Diabetes Diagnosis[13-14] arguments that there exist discrepancies on definitive diabetes diagnosis since a baseline fasting glycemia > 126 mg/dL and glycemia >200 mg/dL after an OGOT usually identify the same individuals, other times both criteria are not present. Thus, in the DECODE Study[25] on 1517 individuals with diabetes diagnosed by means of any of the two criteria, only 28% of the patients met the two of them; 40% met only the baseline glycemia > 126 mg/dL criterion, and 31% met the glycemia > 200 mg/dL at 2 hours after OGOT criterion. In the same way, in the NHANES III Study[14] with 2821 individuals aged 40 to 74 years, and previously not diagnosed with diabetes, 44% met both criteria, 14% only the one for baseline fasting glycemia > 126 mg/dL, and 41% the one for OGOT separately; that is to say, a high percentage of individuals were diagnosed with diabetes only after the OGOT was done. In agreement with this data, of patients with normal baseline glycemia, 38% had OGI after OGOT and up to 5% had diabetes criteria, and of patients with abnormal baseline glycemia, 33% had OGI and 21% diabetes.

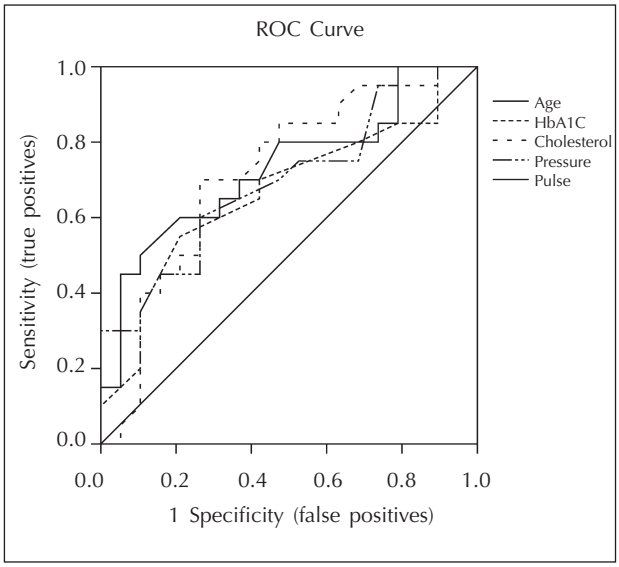

Fig. 1.—Comparison of the relationship between the rate of true positive (sensitivity) and false positive (1-specificity) for age, HbA1C, total cholesterol, and pulse pressure as predictors of an abnormal OGOT (glycemia within 2 hours ≥ 140 m/dl).

According to the Experts Committee for the Diagnosis and Classification of Diabetes,[13-14] asymptomatic individuals in whom diabetes screening should be done (by means of baseline glycemia or OGOT) are: subjects older than 45 years, particularly those with BMI > 25 kg/m^2, subjects younger than 45 years with BMI > 25 kg/m^2 and having additional risk factors

Table III. Area under the ROC curve for the different clinical and metabolic markers of abnormal OGOT

	Area under the curve	95% CI	p
Age	0,716 ± 0.086	0.546-0.885	.015
Hb A1C	0.664 ± 0.092	0.483-0.845	.072
Total Cholest.	0.725 ± 0.088	0.553-0.897	.020
Pulse pressure	0.698 ± 0.087	0.527-0.870	.034

Abnormal OGOT: after oral glucose overload, glycemia within 2 hours ≥ 140 mg/dL. Total Cholest. = Total cholesterol.

such as diabetic first-degree relatives, sedentary lifestyle, ethnicity at risk for diabetes, women with children with high weight at birth or with gestational diabetes, arterial hypertension, HDL cholesterol < 35 mg/dL or triglycerides > 250 mg/dL, polycystic ovaries, and personal history of vascular disease. Surprisingly, renal patients, most of which are hypertensive or have associated vascular disease or have peripheral insulin resistance are not included. It may be thought that this group of patients may benefit from early detection of these metabolic abnormalities given the high cardiovascular risk associated with renal disease itself.[26-27]

The high prevalence of metabolic syndrome in our patients is striking, with almost half of the patients with baseline glycemia higher than 100 mg/dL and centrally distributed body fat. The Autonomous Community of the Canary Islands is one of the Spanish communities with the highest frequencies of diabetic patients at the dialysis units.[28-29] It is not exactly known whether this is due to ha higher diabetes mellitus prevalence or to a higher rate of occurrence of complications from it. The high percentage of our patients with occult diabetes diagnosed by means of OGOT may have a relationship with a higher genetic or environmental predisposition of our population for diabetes or its complications. It would be interesting to know whether other nephrology units with similar characteristics confirm the findings observed in our study.

Renal function measured by the Cockcroft-Gault index was negatively correlated with glycemia at 2 hours from OGOT, and plasma creatinine was positively correlated with baseline insulin, C peptide, and the HOMA index. Also, proteinuria was positively correlated with baseline glycemia and C peptide, even after excluding those patients newly diagnosed with diabetes by means of OGOT. These findings suggest that early changes in carbohydrate metabolism are associated with renal failure and the greater the peripheral insulin resistance the worse renal function is in our patients.[30-32] It still has to be known whether these changes are secondary to renal failure itself or, on the contrary, they favor renal damage and its progression. In fact, recently studies have been published chronologically relating the pre-diabetes status with later development of renal failure.[31,33]

The role played by peripheral insulin resistance in the development of cardiovascular complications in the general population and the uremic population[34-39] is well known; in fact, our patients with abnormal OGOT had higher percentages of coronary heart disease, higher pulse pressure, and higher use of hypotensive drugs, all this probably being a consequence of the association existing between metabolic syndrome, micro-inflammation, oxidative stress, and accelerated atheromatosis.[40,41] In this sense, Ohya *et al.* have recently published a study on more than 3500 subjects in which they observed a strong association between velocity of the pulse wave, proteinuria, and the different degrees of renal failure independently of other known cardiovascular risk factors.[41]

To our knowledge, this is the first work that, based on the ROC curves model, has been able to identify those clinical conditions that are more likely to detect carbohydrate metabolism changes and even occult diabetes in this type of patients with advanced CRF; it would be interesting to verify these findings in other groups.

We are aware of the limitations of our study regarding the number of studied patients, but it may establish the bases for starting prospective studies analyzing whether these metabolic changes occurring at advanced stages of chronic renal failure have intermediate-term consequences on global or cardiovascular mortality of the patient once dialysis has been started or accelerate renal function worsening and entering into dialysis, or whether these changes treated at early pre-dialysis stages may be reverted with weight loss measures, physical activity, or drugs increasing the sensitivity to insulin such as metformin or acarbose.

CONCLUSIONS

Fasting baseline glycemia does not predict an abnormal OGOT in patients with advanced CRF. OGOT may be a useful tool in identifying "pre-diabetic" states and diabetes in patients with advances CRF, especially those presenting higher cardiovascular risk, high pulse pressure (higher than 66 mmHg), older age (> 65 years), dyslipidemia and HbA1C higher than 5%. Early detection of these abnormalities will prone us to intensify dietary and pharmacological measures focused on delaying or decreasing diabetes onset and

its severe complications in a population, such as the uremic one, in which cardiovascular risk is very high.

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